Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/GB05/000800

International filing date: 04 March 2005 (04.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0412262.8
Filing date: 02 June 2004 (02.06.2004)

Date of receipt at the International Bureau: 07 April 2005 (07.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

PCT/GB 2005 / 0 0 0 8 0 0

GB05/800

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed

Dated 18 March 2005

Patents Form 1/77
Patents Act 1977
(Rule 16)

THE PATENT OFFICE
Patent Office
- 2 JUN 2004
LONDON

03JUN04 E900591-3 001631
P01/7700 0.00-0412262.8 NONE

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form.)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

Fee: £

1. Your reference — 47524.GB01/NT

- 2 JUN 2004

2. Patent application number *(The Patent Office will fill in this part)* — 0412262.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Cambridge Biotechnology Ltd
P.O. Box 230
Cambridge
CB2 1XJ
United Kingdom

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of incorporation — United Kingdom

8205761002

4. Title of the invention — Use of Compounds for the Treatment of Pain

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

Patents ADP number *(if you know it)* — 91001

6. If you are declaring priority from one or more earlier patent applications, give the country

Country	Priority application *(If you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application,

Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
   See note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document.

Continuation sheets of this form	-
Description	9
Claim(s)	4
Abstract	-
Drawing(s)	2 + 2 &m.

10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature(s) Peddie e Goose Date 1 June 2004

12. Name and daytime telephone number of person to contact in the United Kingdom

N THORNTON
01223 -360 650

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

47524.GB01

Use of Compounds for the Treatment of Pain

This invention relates to use of compounds for the prevention, treatment, or amelioration of ischaemic pain.

Known analgesics include opiates, and non-steroidal anti-inflammatory drugs (NSAIDs). However, opiates cause undesirable side effects (such as restlessness, nausea, and vomiting) and are addictive. NSAIDs cause irritation of the gastro-intestinal tract. Other known analgesics include adenosine receptor agonists. However, adenosine receptor agonists cause widespread vasodilation with consequent hypotension and tachycardia, and selective A1 receptor agonists cause bradycardia. There is, therefore, a need to provide analgesics that are not addictive and do not have serious side effects.

Spongosine was first isolated from the tropical marine sponge, *Cryptotethia crypta* in 1945 (Bergmann and Feeney, J. Org. Chem. (1951) 16, 981, Ibid (1956) 21, 226), and was the first methoxypurine found in nature. It is also known as 2-methoxyadenosine, or 9H-purin-6-amine, 9-α-D-arabinofuranosyl-2-methoxy. The first biological activities of spongosine were described by Bartlett *et al.* (J. Med. Chem. (1981) 24, 947-954) who disclosed that this compound has muscle relaxant, hypothermic, hypotensive, and anti-inflammatory activity (anti-inflammatory activity was determined using the rat paw edema model) in rats.

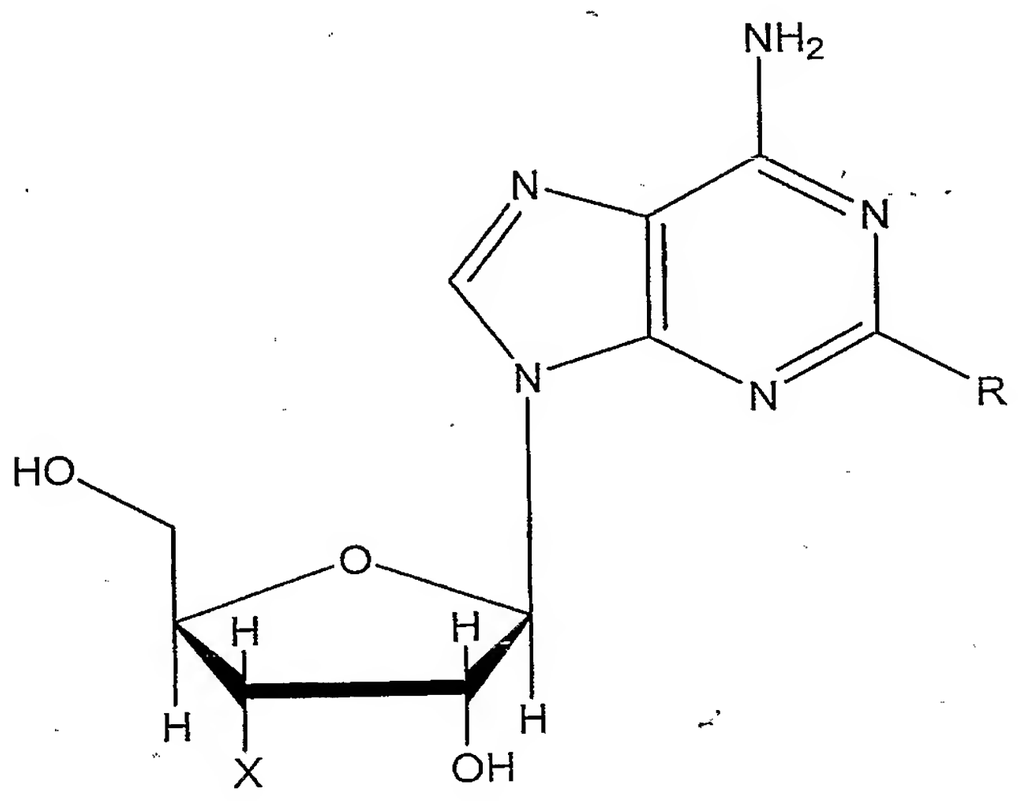
The affinity of spongosine for the rat adenosine A1 and A2A receptors has been determined. The Kd values obtained (in the rat) were 340nM for the A1 receptor and 1.4μM for the A2A receptor, while the EC50 value for stimulation of the rat A2A receptor was shown to be 3μM (Daly *et al.*, Pharmacol. (1993) 46, 91-100). In the guinea pig, the efficacy of spongosine was tested in the isolated heart preparation and the EC50 values obtained were 10 μM and 0.7 μM for the adenosine A1 and A2A receptors, respectively (Ueeda et al J Med Chem (1991) 34, 1334-1339). Because of the low potency and poor receptor selectivity of this compound it was largely ignored in favour of more potent and receptor selective adenosine receptor agonists.

It has surprisingly been found that spongosine is an effective analgesic at doses as much as one hundred times lower than would be expected to be required based on the known affinity of this compound for adenosine receptors. At these doses, spongosine does not cause the significant side effects associated with higher doses of this compound, or other adenosine receptor agonists. The activity of spongosine and related compounds as analgesics is the subject of International patent application nos. PCT/GB03/05379 and PCT/GB04/00935 (unpublished at the filing date of the present application).

It has now been appreciated that spongosine may be effective in the prevention, treatment, or amelioration of ischaemic pain. It is believed that compounds related to spongosine may also be effective against ischaemic pain.

According to the invention there is provided use of a compound of formula (I) in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain:

(I)



wherein R is C_{1-4} alkoxy, and X is H or OH. Preferably R is C_{1-4} alkoxy, and X is OH.

There is also provided according to the invention a method of preventing, treating, or ameliorating ischaemic pain, which comprises administering a compound of formula (I) to a subject in need of such prevention, treatment, or amelioration.

The term "ischaemic pain" is used herein to mean pain associated with a reduction in blood supply to a part of the body. A reduced blood supply limits the supply of oxygen (hypoxia) and energy to that part of the body. Ischaemia arises from poor blood perfusion of tissues and so ischaemic pain arises in coronary artery disease, peripheral artery disease, and conditions which are characterized by insufficient blood flow, usually secondary to atherosclerosis. Other vascular disorders can also result in ischaemic pain. These include: left ventricular hypertrophy, coronary artery disease, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncopy, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis oblitterens), arteritis, diastolic dysfunction and systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (both Types I and II), thromboembolisms. Haemorrhagic accidents can also result in ischaemic pain. In addition poor perfusion can result in neuropathic and inflammatory pain arising from hypoxia-induced nerve cell damage (e.g. in cardiac arrest or bypass operation, diabetes or neonatal distress).

Preferred compounds of formula (I) are 2-methoxyadenosine, 2-ethoxyadenosine, and 2-butyloxyadenosine.

Compounds of formula (I) are believed to be effective in prevention, treatment, or amelioration of ischaemic pain even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. At these doses, it is believed that the compounds do not cause the significant side effects associated with administration of higher doses of spongosine, or other adenosine receptor agonists.

The amount of a compound of formula (I) that is administered to a subject is preferably an amount which gives rise to a peak plasma concentration that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.

It will be appreciated that the EC50 value of the compound is likely to be different for different adenosine receptors (i.e. the A1, A2A, A2B, A3 adenosine receptors). The amount of the compound that is to be administered should be calculated relative to the lowest EC50 value of the compound at the different receptors.

Preferably the peak plasma concentration is one thousandth to one fifth, or one fiftieth to one third (more preferably one thousandth to one twentieth, one hundredth or one fiftieth to one fifth, one fiftieth to one tenth, or one tenth to one fifth) of the EC50 value. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour between one thousandth and one fifth, or one thousandth and one twentieth, or one hundredth and one fifth, or one fiftieth and one fifth, of the EC50 value of the compound at adenosine receptors at pH 7.4.

For the avoidance of doubt, the EC50 value of a compound is defined herein as the concentration of the compound that provokes a receptor response halfway between the baseline receptor response and the maximum receptor response (as determined, for example, using a dose-response curve).

The EC50 value should be determined under standard conditions (balanced salt solutions buffered to pH 7.4). For EC50 determinations using isolated membranes, cells and tissues this would be in buffered salt solution at pH 7.4 (e.g. cell culture medium), for example as in (Daly *et al.*, Pharmacol. (1993) 46, 91-100), or preferably as in Tilburg *et al* (J. Med. Chem. (2002) *45*, 91-100). The EC50 could also be determined *in vivo* by measuring adenosine receptor mediated responses in a normal healthy animal, or even in a tissue perfused under normal conditions (i.e. oxygenated blood, or oxygenated isotonic media, also buffered at pH 7.4) in a normal healthy animal.

Alternatively, the amount of a compound of formula (I) that is administered may be an amount that results in a peak plasma concentration that is one thousandth to one twentieth, one thousandth to one third, more preferably one hundredth to one fifth, or one fiftieth to one tenth, of the Kd value at adenosine receptors.

It will be appreciated that the Kd value of the compound is likely to be different for different adenosine receptors (i.e. the A1, A2A, A2B, A3 adenosine receptors). The amount of the compound that is to be administered should be calculated relative to the lowest Kd value of the compound for the different receptors.

Preferably the amount of the compound that is administered is an amount that results in a plasma concentration that is maintained for at least one hour between one thousandth and one fifth, more preferably between one thousandth and one twentieth, or one hundredth and one fifth, or one fiftieth and one fifth, of the Kd value of the compound at adenosine receptors.

The Kd value of the compound at each receptor should be determined under standard conditions using plasma membranes as a source of the adenosine receptors derived either from tissues or cells endogenously expressing these receptors or from cells transfected with DNA vectors encoding the adenosine receptor genes. Alternatively whole cell preparations using cells expressing adenosine receptors can be used. Labelled ligands (e.g. radiolabelled) selective for the different receptors should be used in buffered (pH7.4) salt solutions (see e.g. Tilburg et al, J. Med. Chem. (2002) 45, 420-429) to determine the binding affinity and thus the Kd of the compound at each receptor.

Alternatively, the amount of a compound of formula (I) that is administered may be an amount that is one thousandth to one fifth, or one fiftieth to one third (preferably one thousandth to one twentieth, or one hundredth or one fiftieth to one fifth) of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount is one tenth to one fifth of the minimum dose that gives rise to the side effects. Preferably the amount administered

gives rise to a plasma concentration that is maintained for more than 1 hour between one thousandth and one twentieth, or one hundredth or one fiftieth and one fifth of the minimum dose that gives rise to the side effects.

Alternatively, the amount of a compound of formula (I) that is administered may be an amount that gives rise to plasma concentrations that are one thousandth to one fifth, or one fiftieth to one third (preferably one thousandth to one twentieth, or one hundredth or one fiftieth to one fifth) of the minimum plasma concentration of the compound that cause bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount gives rise to plasma concentrations that are one tenth to one fifth of the minimum plasma concentration that causes the side effects. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than 1 hour between one thousandth and one twentieth, or one hundredth or one fiftieth and one fifth, of the minimum plasma concentration that causes the side effects.

It is expected that the amount of a compound of formula (I) that is administered should be 0.01 to 15 mg/kg, for example 0.01 to 5 or 10 mg/kg. Preferably the amount is less than 6 mg/kg, for example 0.01 to 2 mg/kg. Preferably the amount is at least 0.01 or 0.1 mg/kg, for example 0.1 to 2 mg/kg, or 0.2 to 1 mg/kg. A typical amount is 0.2 or 0.6 to 1.2 mg/kg.

Preferred doses for a human subject (for example a 70kg subject) are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least 7mg. More preferably 7 to 70mg, or 14 to 70mg.

The dosage amounts specified above are aimed at producing plasma concentrations that are approximately one thousandth to one hundredth of the EC50 value of spongosine at the adenosine A1 receptor.

The appropriate dosage of a compound of formula (I) will vary with the age, sex, weight, and condition of the subject being treated, the potency of the compound, and

the route of administration, etc. The appropriate dosage can readily be determined by one skilled in the art.

A compound of formula (I) may be administered with or without other therapeutic agents, for example analgesics or anti-inflammatories (such as opiates, steroids, NSAIDs, cannabinoids, tachykinin modulators, or bradykinin modulators) or anti-hyperalgesics (such as gabapentin, pregabalin, cannabinoids, sodium or calcium channel modulators, anti-epileptics or anti-depressants).

In general, a compound of formula (I) may be administered by known means, in any suitable formulation, by any suitable route. A compound of the invention is preferably administered orally, parenterally, sublingually, transdermally, intrathecally, or transmucosally. Other suitable routes include intravenous, intramuscular, subcutaneous, inhaled, and topical. The amount of drug administered will typically be higher when administered orally than when administered, say, intravenously.

It will be appreciated that a compound of formula (I) may be administered together with a physiologically acceptable carrier, excipient, or diluent.

Suitable compositions, for example for oral administration, include solid unit dose forms, and those containing liquid, e.g. for injection, such as tablets, capsules, vials and ampoules, in which the active agent is formulated, by known means, with a physiologically acceptable excipient, diluent or carrier. Suitable diluents and carriers are known, and include, for example, lactose and talc, together with appropriate binding agents etc.

A unit dosage of a compound of the invention typically comprises up to 500 mg (for example 1 to 500 mg, or 5 to 500 mg) of the active agent. Preferably the active agent is in the form of a pharmaceutical composition comprising the active agent and a physiologically acceptable carrier, excipient, or diluent. The preferred dosage is 0.1 to 2, e.g. 0.5 to 1, typically about 0.2 or 0.6, mg of the active agent per kg of the (human) subject. Preferred amounts of the active agent are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least

7mg. More preferably 7 to 70mg, or 14 to 70mg. At these levels, it is believed that effective treatment can be achieved substantially without a concomitant fall (for example, no more than 10%) in blood pressure.

Preferably a compound of formula (I) is administered at a frequency of 2 or 3 times per day.

Use of a compound of formula (I) in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain, or a method of prevention, treatment, or amelioration of ischaemic pain by administering a compound of formula (I) in accordance with the invention may exclude prevention, treatment, or amelioration of pain resulting from damage caused to organs as a consequence of reperfusion following an ischaemic episode, for example a myocardial infarct, or a stroke.

Use of a compound of formula (I) in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain in accordance with the invention may exclude use of 2-propoxyadenosine, 2-isopropoxyadenosine, 3' deoxy 2 methoxyadenosine or 3' deoxy 2 ethoxyadenosine.

A method of prevention, treatment, or amelioration of ischaemic pain by administering a compound of formula (I) in accordance with the invention may exclude use of 2-propoxyadenosine, 2-isopropoxyadenosine, 3' deoxy 2 methoxyadenosine or 3' deoxy 2 ethoxyadenosine.

Embodiments of the invention are described in the following examples with reference to the accompanying drawings in which:

Figure 1 shows the effect of spongosine (0.6 mg/kg p.o.) on A: blood pressure in normal rats; B: heart rate; and

Figure 2 shows the change in plasma concentration over time after administration of spongosine.

Examples

Example 1

Figure 1: Spongosine (0.624 mg/kg p.o.) has no significant effect on blood pressure or heart rate. An implantable radiotelemetry device was placed in the abdominal cavity of 6 rats per group. The pressure catheter of the device was inserted in the abdominal aorta and two electrodes tunnelised under the skin in a lead II position (left side of abdominal cavity/right shoulder). Individual rats were placed in their own cage on a radioreceptor (DSI) for data acquisition. A: blood pressure; B: heart rate.

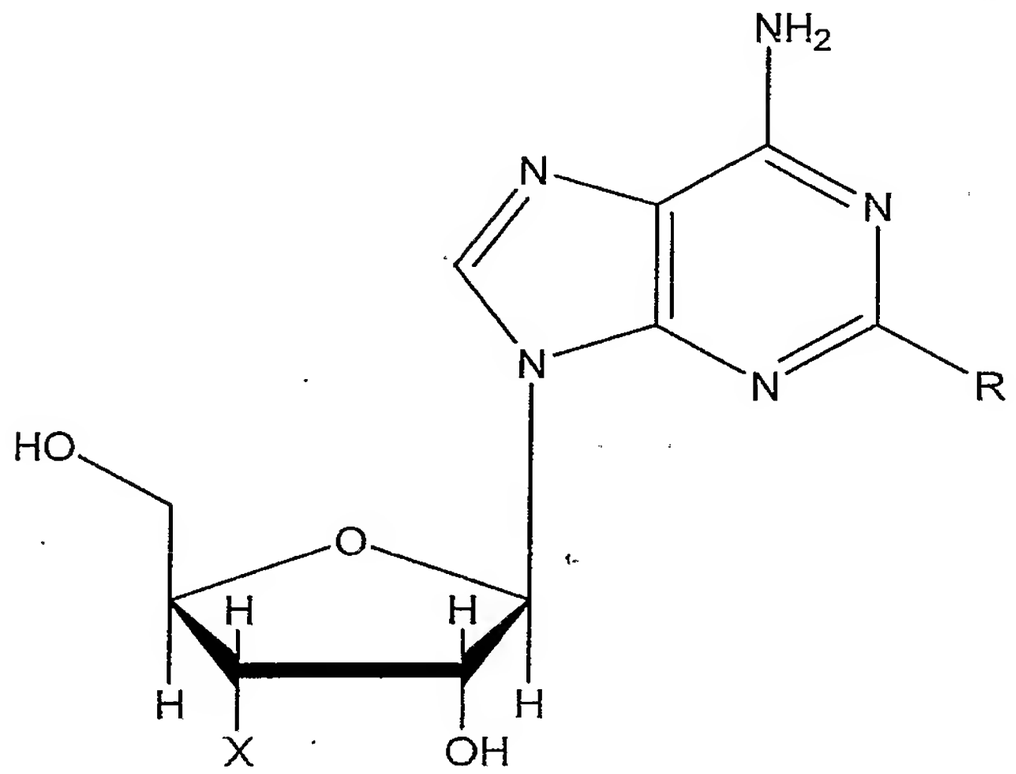
Example 2

The EC50 value of spongosine at adenosine receptors (measured at pH7.4) is 900ng/ml (3 μM). Figure 2 shows the change in plasma concentration over time after administration of spongosine at 0.6 mg/kg to a rat. It can be seen that the plasma concentration remains above 2% of the EC50 value for more than 3 hours. Anti-hyperalgesic effects have been observed (without blood pressure changes) when the peak plasma concentration is between 1% and 30% of the EC50 value determined in vitro. If the peak plasma concentration reaches the EC50 value profound reductions in blood pressure occur that last for hours.

Claims

1. Use of a compound of formula (I) in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain:

(I)



wherein R is C_{1-4} alkoxy, and X is H or OH.

2. Use according to claim 1 at a dosage which, after administration to a subject, gives rise to a peak plasma concentration of the compound that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.

3. Use according to claim 1 or 2 at a dosage that is one thousandth to one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.

4. Use according to claim 3, wherein the dose is one hundredth to one fifth of the minimum dose that gives rise to the side effects.

5. Use according to any preceding claim at a dosage which, after administration to a subject, gives rise to a plasma concentration of the compound that is maintained

for more than one hour between one thousandth and one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.

6. Use according to any preceding claim, at a dosage of less than 6mg/kg.

7. Use according to any preceding claim at a dosage of at least 0.01mg/kg.

8. Use according to any preceding claim at a dosage of 0.2 to 1mg/kg.

9. Use according to any preceding claim in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain associated with coronary artery disease, peripheral artery disease, left ventricular hypertrophy, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncopy, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis oblitterens), arteritis, diastolic dysfunction, systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (Types I or II), thromboembolisms, haemorrhagic accidents, or neuropathic or inflammatory pain arising from hypoxia-induced nerve cell damage.

10. A method of preventing, treating, or ameliorating ischaemic pain which comprises administering a compound of formula (I) to a subject in need of such prevention, treatment, or amelioration.

11. A method according to claim 10, wherein the compound is administered at a dose that gives rise to a peak plasma concentration of the compound that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.

12. A method according to claim 10, wherein the compound is administered at a dose that is one thousandth to one fifth of the minimum dose of the compound that

gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the dose is to be administered.

13. A method according to claim 12, wherein the dose is one hundredth to one fifth of the minimum dose that gives rise to the side effects

14. A method according to any of claims 10 to 13, wherein the compound is administered at a dose that results in a plasma concentration of the compound that is maintained for more than one hour between one hundredth and one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.

15. A method according to any of claims 10 to 14, wherein the compound is administered at a dose of less than 6mg/kg.

16. A method according to any of claims 10 to 15, wherein the compound is administered at a dose of at least 0.01mg/kg.

17. A method according to any of claims 10 to 16, wherein the compound is administered at a dose of 0.2 to 1mg/kg.

18. A method according to any of claims 10 to 17, wherein the compound is administered orally, parenterally, sublingually, transdermally, intrathecally, transmucosally, intravenously, intramuscularly, subcutaneously, topically, or by inhaling.

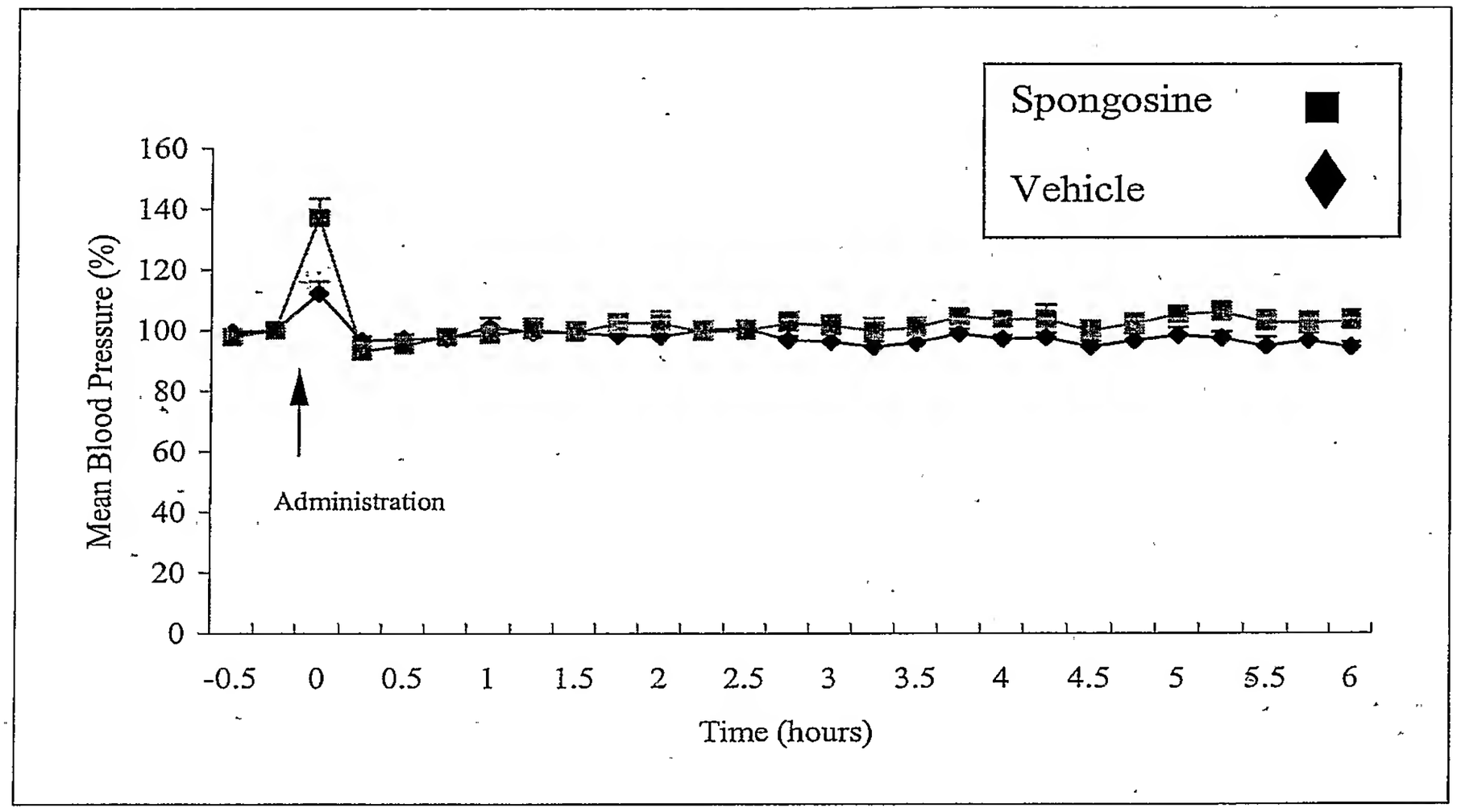
19. A method according to any of claims 10 to 18, wherein the compound is administered at a frequency of 2 or 3 times per day.

20. A method according to any of claims 10 to 19, wherein the subject is a human subject.

21. A method according to any of claims 10 to 20 for the prevention, treatment, or amelioration of ischaemic pain associated with coronary artery disease, peripheral artery disease, left ventricular hypertrophy, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncopy, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis oblitterens), arteritis, diastolic dysfunction, systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (Types I or II), thromboembolisms, haemorrhagic accidents, or neuropathic or inflammatory pain arising from hypoxia-induced nerve cell damage.

Figure 1

A)


Spongosine
Vehicle
Mean Blood Pressure (%)
160
140
120
100
80
60
40
20
0
Administration
-0.5
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
Time (hours)

B)

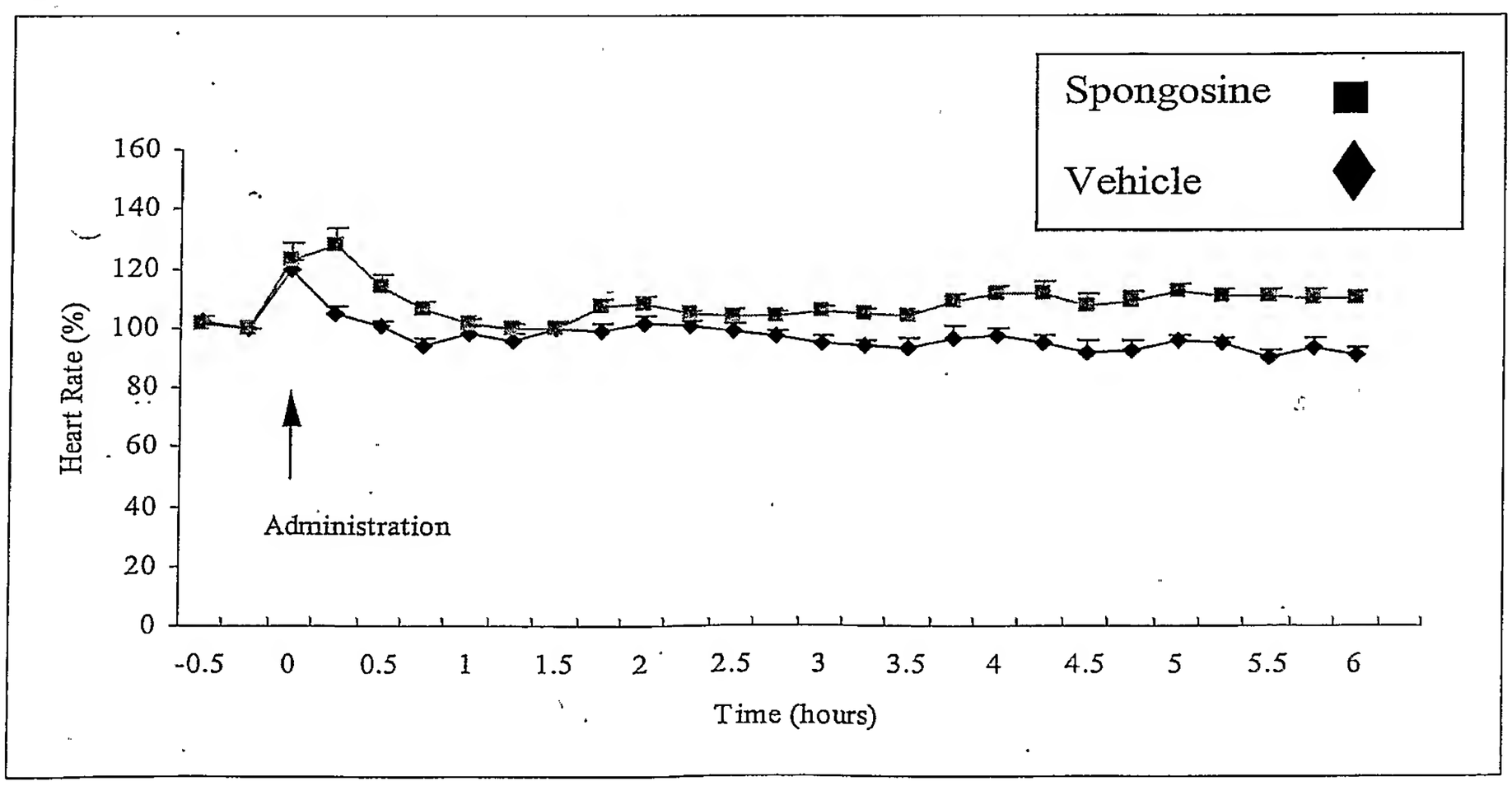
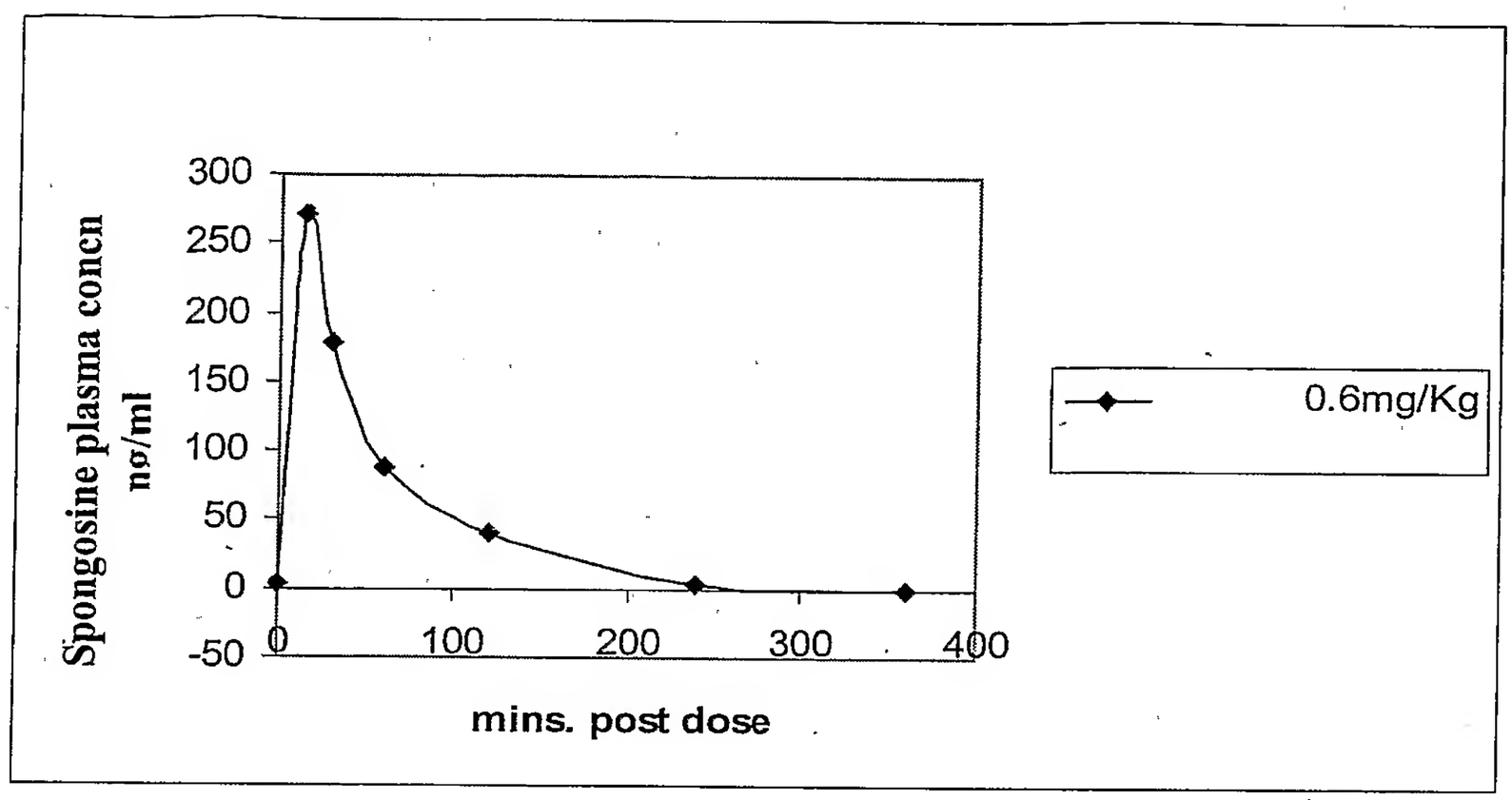

Spongosine
Vehicle
Heart Rate (%)
160
140
120
100
80
60
40
20
0
Administration
-0.5
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
Time (hours)

Figure 2


Spongosine plasma conc ng/ml
300
250
200
150
100
50
0
-50
0
100
200
300
400
mins. post dose
0.6mg/Kg